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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,043	04/03/2000	BERND EIKMANNS	21437	6651

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,043	EIKMANNS ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64,65,70-78 and 81-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64,65,70-78,81-83 and 85-90* is/are rejected.

7)☒ Claim(s) *84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 64-65, 70-78, and 81-90 are pending in the application.

[2] Applicants' amendment to the claims, filed September 02, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Priority

[3] Applicants' claim to foreign priority under 35 USC 119(a)-(d) to German applications 19743894.6, filed October 04, 1997, and 19831609.7, filed July 14, 1998, is acknowledged. English-language translations of the above-identified German patent applications have been filed in the instant application on January 29, 2002.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[4] Claim(s) 70-74, 76, 78, 89, and 90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 70 (claim 73 dependent therefrom) is confusing in the recitation of "a preceding promoter of the nucleotide sequence from nucleotide 20 to 109 according to

SEQ ID NO:1." It is unclear as to whether the term is to be interpreted as meaning the promoter precedes nucleotides 20 to 109 of SEQ ID NO:1 or that the promoter is nucleotides 20 to 109 of SEQ ID NO:1. It is suggested that applicants clarify the meaning of the claim.

[b] Claims 71-72 are indefinite in the recitation of "tac promoter" as it is unclear from the specification and the claims as to the scope of promoters that are encompassed by the terms. For example, what characteristics distinguish a "tac promoter" from other promoters such that one can determine the scope of recited "tac" promoters.

[c] Claims 72-74 are indefinite in the recitation of "a regulatory gene sequence." It is unclear from the specification and the claims as to the scope of gene sequences that are encompassed by the term "regulatory gene sequence." Further, regarding claims 72 and 74, it is unclear as to how this sequence is "associated" with the recited promoter, *e.g.*, is the association a physical association or an association wherein the "regulatory gene sequence" in conjunction with the promoter is involved in promoting transcription?

[d] Claim 74 is indefinite in the recitation of "[a] nucleic acid comprising an isolated pyruvate carboxylase gene" as it is unclear as to how a skilled artisan is to distinguish between the scope of nucleic acids comprising a non-isolated pyruvate carboxylase gene from the scope of nucleic acids comprising an isolated pyruvate carboxylase gene. In other words, what characteristics distinguish those nucleic acids that comprise a non-isolated pyruvate carboxylase gene that are found in nature from the scope of nucleic acids that comprise an isolated pyruvate carboxylase gene? It is suggested that applicants clarify the meaning of the claim.

[e] Claims 76 (claim 78 dependent therefrom) and 89-90 are indefinite as it is unclear as to whether the transformed cell is transformed with, *e.g.*, a vector comprising the isolated pyruvate carboxylase gene, or if it is transformed with some other nucleic acid. If the cell is transformed a nucleic acid other than the isolated pyruvate carboxylase gene, it is unclear as to how one of skill distinguishes between a transformed cell containing an isolated pyruvate carboxylase gene from a transformed cell containing a non-isolated pyruvate carboxylase gene. In other words, what characteristics distinguish those transformed cells comprising an isolated pyruvate carboxylase gene from the scope of transformed cells comprising a non-isolated pyruvate carboxylase gene? It is suggested that applicants clarify the meaning of the claim.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[5] Claims 64-65, 70-78, 81, and 87-90 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to or recite a genus of pyruvate carboxylase genes encoding SEQ ID NO:2 or comprising nucleotides of SEQ ID NO:1. The specification provides no definition of the term "gene" and in accordance with MPEP 2111, the term has been interpreted as encompassing naturally occurring regulatory elements and untranslated regions that mediate the expression of a pyruvate carboxylase. In view of the recitation of "gene," these elements and regions are an essential to the function of the claimed invention. The art indicates that such elements and regions are empirically determined and are not conventional in the art. In this case, there is no known or disclosed correlation between the function of a pyruvate carboxylase and the structure of the non-described regulatory elements and untranslated regions of the claimed or recited gene. Thus, one would recognize that applicants were not in possession of the genus of claimed or recited pyruvate carboxylase genes as encompassed by the claims. See Example 6 of the Revised Interim Written Description Guidelines Training Materials.

[6] Claims 64-65, 71-78, 81-83, 85, and 87-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the isolated nucleic acid of SEQ ID NO:1 and the isolated polypeptide of SEQ ID NO:2, does not reasonably provide enablement for all pyruvate carboxylase genes of SEQ ID NO:1 or encoding SEQ ID NO:2 or polypeptides having at least 95% identity to SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: Regarding claims 64-65, 70-78, 81, and 87-90, the claims are so broad as to encompass pyruvate carboxylase genes, encompassing naturally occurring regulatory elements and untranslated regions associated with the recited nucleic acid sequence, *i.e.*, a nucleic acid encoding SEQ ID NO:2 or the nucleic acid of SEQ ID NO:1, that mediate the expression of a pyruvate carboxylase polypeptide. Further, the claims optionally encompass nucleic acids comprising additional promoters and/or regulatory gene sequences having any nucleic acid sequence(s). Regarding claims 82-83 and 85, the claims are so broad as to encompass numerous variants of the polypeptide of SEQ ID NO:2, including variants having substitution(s), deletion(s), addition(s), and insertion(s) of SEQ ID NO:2 within the recited identity limitation. The broad scope of claimed pyruvate carboxylase genes

and polypeptides is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to the isolated nucleic acid of SEQ ID NO:1 and the isolated polypeptide of SEQ ID NO:2.

- The lack of guidance and working examples: Regarding claims 64-65, 70-78, 81, and 87-90, the specification discloses only a single working example of a nucleic acid encoding SEQ ID NO:2, *i.e.,* SEQ ID NO:1. The specification fails to provide guidance for determining which sequences of the *Coryneform glutamicum* genomic DNA are naturally occurring regulatory elements and untranslated regions associated with SEQ ID NO:1 that mediate the expression of the pyruvate carboxylase polypeptide of SEQ ID NO:2. Furthermore, the specification fails to disclose all regulatory gene sequences that are associated with any promoter or a "tac" promoter. Regarding claims 82-83 and 85, the specification provides only a single working example of the claimed polypeptide, *i.e.,* SEQ ID NO:2. This working example fails to provide the necessary guidance for making and the entire scope of polypeptides. The specification fails to provide guidance regarding those amino acids of SEQ ID NO:2 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the desired pyruvate carboxylase activity.

- The high level of unpredictability in the art: Regarding claims 64-65, 70-78, 81, and 87-90, the amino acid sequence of a protein determines its structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant

of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above.

- The state of the prior art supports the high degree of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). As a representative example of the teachings of Branden et al., Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1,

page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein's sequence with an expectation of obtaining a protein having a desired function and discloses that even a single substitution in a polypeptide's amino acid sequence may completely alter the function of a polypeptide.

- The amount of experimentation required is undue: While methods of determining those regulatory sequences responsible for gene expression are known in the art, it is not routine to screen for all such sequences, which may or may not be in close proximity to a coding sequence. Further, while methods of generating variants of a given polypeptide, *e.g.,* mutagenesis, and methods of isolating homologous polypeptide-encoding nucleic acids, *e.g.,* hybridization, are known, it is not routine in the art to screen for all polypeptides having a substantial number of substitutions or modifications as encompassed by the instant claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and/or use all pyruvate carboxylase genes and polypeptides as encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the

desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

[7] Claims 82-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn (in part) to a polypeptide encoded by a novel bacterial strain (ATCC 13032). Since the microorganism comprises a vector that is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The vector's sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the vector. The specification does not disclose a repeatable process to obtain the vector and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of the vector should have been made in accordance with 37 CFR 1.801-1.809.

If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction

or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

1. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

2. all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

3. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

4. the deposit will be replaced if it should ever become inviable.

Claim Objections

[8] Claim 81 is objected to in the use of the improper sequence identifier "SEQ ID No." It is suggested that applicants replace this sequence identifier with the proper sequence identifier "SEQ ID NO:".

[9] Claim(s) 82 and 85-86 are objected to in the recitation of "pEKO pyc" as the vector that is referred to by applicants as "pEKO pyc" in claims 82 and 85-86 is listed as

"pEK0pyc" (note the use of zero ("0") and not the letter "O") in the specification (see, *e.g.*, p. 14).

[10] Claim 84 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Clarification

[11] It is noted that claims 82-83 and 85 are drawn to an "isolated pyruvate carboxylase polypeptide." The examiner has given the claims their broadest reasonable interpretation in light of the specification. It is noted that there is no indication in the disclosure of the specification that a "pyruvate carboxylase polypeptide" is meant to encompass polypeptides that do not have pyruvate carboxylase enzyme activity. As the claimed polypeptides are limited to those that are pyruvate carboxylase polypeptides, the claims have been interpreted as meaning that all polypeptides encompassed by the scope of polypeptides of claims 82-83 and 85 have pyruvate carboxylase enzymatic activity.

Conclusion

[12] Status of the claims:

- Claims 64-65, 70-78, and 81-90 are pending.
- Claims 64-65, 70-78, 81-83, and 85-90 are rejected.

- Claim 84 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

- No claim is in condition for allowance.

- Claims 64-65, 70-78, and 81-90 would be allowable if rewritten to overcome the rejection(s) set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

11-09-04

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652